REMARKS

In view of the foregoing amendments, reconsideration and withdrawal of the outstanding Office Action rejections is respectfully requested. Claims 1-236 have been cancelled and claims 237-294 have been added. No new matter has been added.

Response to Priority

The Office Action states that disclosure of prior-filed application 60/094,690, filed July 30, 1998, fails to provide adequate written description support for the claims. Applicants submit that the claims, as amended, are supported in the manner provided by 35 U.S.C. § 112, first paragraph, by the disclosure in U.S. 60/094,690.

For example, with regard to the presently recited independent claims, U.S. 60/094,690 provides written description support for the present claims, *inter alia*, as follows:

Support for tissue repair and regeneration, *inter alia*, is found on page 3, lines 19-21, the paragraph bridging pages 6 and 7, and page 7 (as a whole).

Support for systemic administration, *inter alia*, is found on page 3, lines 23-25, page 4, lines 11-14 and lines 18-21, page 9, line 14, and Example 1 on page 23.

Support for topical administration, *inter alia*, is found on page 4, lines 11-17 and lines 21-23, page 9, line 14, and Example 1 on page 23.

Support for a method of systemically administering 60 μg Tβ4 to effect tissue repair is found, *inter alia*, on page 23, line 24, and Figures 2-5.

Support for a method of topically administering 5 μg Tβ4 to effect tissue repair is found, *inter alia*, on page 23, line 24 and Figures 2-5.

Support for administering Tβ4 with a pharmaceutically acceptable carrier is found, inter alia, on page 16, lines 21-23.

Applicants respectfully request that the Examiner acknowledge the Applicant's priority benefit in this application from U.S. 60/094,690.

Response to Rejections under 35 U.S.C. § 102

Claims 187-188, 192-193, 195-196, 200, 202-205, 209-210, 212-213, 217, 219-221, and 223 were rejected under 35 U.S.C. § 102(b) as being anticipated by Turischev as evidenced by Mann. Insofar as this rejection could apply to the present claims, it is respectfully traversed.

In the Office Action, it is asserted that Turischev discloses that 'thymosin' is effective in healing flat skin wounds in rats. The Office Action asserts that Turischev disclose results of experiments involving removing a skin flap from the backs of rats and administering Thymosin Fraction 5 (TF5) to the rats, either intraperitoneally or topically. The Office Action asserts that Turischev discloses that there is clear acceleration of the healing rates and that a dose of 0.8 μg accelerated wound healing.

The Office Action acknowledges that Turischev does not recite the components of thymosin 5 fraction, but asserts that Mann discloses (column 4 lines 8-53) that thymosin fraction 5 contains thymosin beta 4 (column 4 line 31) and thymosin alpha 1 (column 4 line 26). Accordingly, the Office Action asserts that Turischev discloses

administering a composition containing thymosin beta 4 either topically or intraperitoneally. The previously pending claims have been cancelled and replaced with claims 237-294. The newly presented claims are not anticipated by, or even remotely rendered obvious by Turischev as evidenced by Mann.

Claims 237-266, as amended, are directed to a method of promoting repair of a tissue in a subject in need of tissue repair, comprising topically administering to the subject a composition comprising thymosin beta 4 (TB4) and a pharmaceutically acceptable carrier or vehicle therefore, wherein the composition is administered in an amount effective to repair and revitalize the subject's tissue. In contrast to the present invention, Turischev shows that topical administration of TF5 **decreased** wound healing. Turischev discloses that increasing the concentration of TF5 trended towards **further** slowing the healing process (page 5 of translation). Thus, one looking to topically promote tissue repair by administering a composition in an amount effective to repair and revitalize the subject's tissue would not find any disclosure in Turischev anticipating or even remotely suggesting the presently claimed method.

Because Turischev discloses a negative and detrimental result when administering TF5 topically to rats, it is clear that Turischev cannot anticipate the presently claimed method or in any way render it obvious. No tissue repair was disclosed in Turischev. No composition was administered in an amount effective to repair and revitalize tissue, and no wound healing was promoted by topical administration.

Rather, Turischev demonstrated that TF5, administered topically, significantly

inhibits wound healing. Thus, persons of ordinary skill in the art reading Turischev would have found it clear that topical administration of TF5 was detrimental, ineffective, and should be avoided. Accordingly, Applicants submit that independent claim 237 and claims 238-266, depending therefrom, are not anticipated by or rendered obvious by Turischev.

Applicants submit that dependent claim 259, which is directed to an embodiment wherein the composition is administered in an amount effective to revascularize the subject's tissue, is not anticipated by Turischev because Turischev discloses that topical local administration directly to a wound actually decreases the rate of wound closure. Accordingly, no revascularization was disclosed or suggested by Turischev. Written description support for this subject matter is found, *inter alia*, in Figure 4 and on page 5, lines 16-29. No new matter has been added.

Further, Applicants submit that dependent claim 260, which is directed to a method wherein the inventive composition is topically administered in an amount effective to increase revascularization of the tissue by about 2 fold compared to untreated tissue, is not anticipated by Turischev because Turischev discloses that topical administration actually decreases the rate of wound closure. Written description support for this subject matter is found, *inter alia*, in Figure 4 and on page 31, last paragraph. No new matter has been added.

Applicants submit that dependent claim 261, which is directed to a method wherein the composition is topically administered in an amount effective to increase re-epithelialization of tissue by at least 2 fold compared to untreated tissue is not

anticipated by Turischev because Turischev discloses that topical administration actually decreases the rate of wound closure and increases the period for complete epithelialization with increasing doses of TF5 (last paragraph of Turischev). Written description support for this subject matter is found, *inter alia*, on page 34, lines 13-15 and Figures 8 and 9. No new matter has been added.

Applicants submit that dependent claim 262, which is directed to a method wherein said composition contains greater than 5 µg of said TB4 is not anticipated by Turischev because Turischev discloses the use of 0.2, 0.8, and 1.6 µg/g of TF5 in rats weighing between 180 and 220 grams. Accordingly, the largest amount of TF5 administered was 1.6 µg/g x 220 g = 352 µg TF5. The attached declaration of Dr. Ehrlich details that TF5 has long been known to contain 0.45 % thymosin beta 4. Accordingly, the largest amount administered by Turischev was 1.584 µg of thymosin beta 4. Thus, Turischev does not anticipate claim 262. Further, because Turischev discloses that the percentage of symptoms of suppuration increased as the amount of TF5 administered increased, the trend is even more suppuration with increased TF5, and the trend showed that administering 1.6 µg/g would increase the length of time for complete reepithelialization (PCE), Applicants submit that, in addition to teaching away from topical use of TF5, Turischev teaches away from increasing the dose as well. Written description support for this subject matter is found, *inter alia*, on page 5, line 23, page 29, lines 13-15, and Figures 2-4. No new matter has been added.

Further, Applicants submit that dependent claim 263, which is directed to a

method wherein at least 50 µl of said composition is administered topically is not anticipated by Turischev because Turischev demonstrates that applying increasing amounts of TF5 causes negative effects on the wounds of the rats. Written description support for this subject matter is found, *inter alia*, on page 5, line 23, page 29, lines 13-15, and and Figures 2-4. No new matter has been added.

Turischev discloses that each TF5 dose was diluted in 0.5 mL physiological solution before being administered to the rats (see page 2, 1st full paragraph of the translation provided by the U.S. Patent and Trademark Office). Accordingly, the concentrations of Tβ4 in the compositions administered at the 0.2 µg/g, 0.8 µg/g, and 1.6 µg/g doses to the largest rat were 0.2 µg/500 µL, 0.79 µg/500 µL, and 1.58 µg/500 µL, respectively, i.e., 0.04% w/v, 0.16% w/v, 0.32% w/v, respectively. Applicants submit that claim 264, which is directed to a method wherein the composition contains at least 10% thymosin beta 4 (TB4) by w/v is not anticipated by Turischev because Turischev discloses the administration of compositions containing at most 0.32 % w/v TB4. Written description support for this subject matter is found, *inter alia*, in Example 1 on pages 29-32 and Figures 2-4. No new matter has been added.

Further, Applicants submit that dependent claim 265, which is directed to a method wherein the composition is substantially free of other proteins, lipids, or carbohydrates with which TB4 is naturally associated is not anticipated by Turischev because Turischev only discloses administering TF5, which, as a naturally derived

fraction from thymus tissue, contains other naturally associated biological components. Written description support for this subject matter is found, *inter alia*, on page 18, lines 4-6 and compositions used in Example 2. No new matter has been added.

Accordingly, Applicants submit that claims 237-266, which are defined as detailed above, are not anticipated by Turischev as evidenced by Mann.

New claims 267-294 are directed to a method of promoting repair of a tissue in a subject in need of tissue repair, comprising systemically administering greater than 6 µg thymosin beta 4 (TB4) in a composition comprising TB4 and a pharmaceutically acceptable carrier or vehicle therefore to the subject, wherein the composition is administered in an amount effective to repair and revitalize the subject's tissue.

Applicants submit that Turischev discloses traditional healing rather than repair and revitalization. Although as a part of the introduction and background, Turischev mentions that immune cells and immunomodulators are involved in a repair process and regeneration, when describing the actual results of the experiments, Turischev does not state or even imply that any of repair and revitalization took place.

Rather, Turischev describes one instance of accelerated re-epithelialization of the wound with phases of inflammation and fibrous rearrangement of granulation tissue (see page 2, last full paragraph of the translation), culminating in the formation of a scar. The formation of a scar as described in Turischev does not form a nexus with the requirements of the presently recited claims. The presently recited claims require that

the composition be administered in an amount effective to repair **and** revitalize the subject's tissue.

As described in the paragraph bridging pages 11 and 12 of the specification, the present invention revitalizes scar tissue by repairing tissue. For example, if scar tissue forms when a patient recovers from surgery, the wound has healed, but the tissue has not been repaired. Similarly, muscle trauma or tearing will heal over time, but will result in formation of scar tissue, which will then have to be repaired to restore full range of motion and strength to the tissue.

The presently claimed method can be used to repair tissue soon after injury so as to minimize the formation of scar tissue, but can also revitalize scar tissue by effecting tissue repair.

Turischev did not administer TF5 in an amount sufficient to effect tissue repair. Further, Turischev did not suggest repairing **and** revitalizing a subject's tissue. None of the other references cited in this Office Action remedy this deficiency of Turischev. Accordingly, Applicants submit that Turischev does not anticipate the present claims for at least this reason.

Further, it is clear that Turischev only achieved a significant wound healing effect when administering 0.8 µg/g TF5, but achieved no wound healing **above** that amount of 0.8 µg/g TF5. Accordingly, Turischev demonstrated that 0.8 µg/g TF5 was the only effective dose because 0.2 µg/g TF5 and 1.6 µg/g TF5 were both ineffective doses. Because TF5 has been known to contain only 0.45 % TB4, the only effective amount of TB4 disclosed in Turischev is 0.648-0.792 µg (0.8 µg/g x 180 or 220 grams x 0.0045),

which has to be administered intraperitoneally because the only other tested method (topically) was shown to detrimental. None of the other TB4 amounts tested, either higher or lower than 0.648-0.792 µg, were significantly better than treatment with physiological solution (Group IV). Thus, Turischev discloses that a composition containing TB4 in amounts of only 0.648 to 0.792 µg is the only effective wound healing composition. Accordingly, independent claim 267, directed to administering greater than 6 µg TB4 systemically is distinguished over Turischev because the Turischev disclosure indicates no significant effect when using greater than 0.792 µg TB4. Accordingly, Applicants submit that Turischev does not anticipate or render obvious the present claims for this reason as well.

Applicants submit that dependent claim 270, which is directed to a method wherein the effective amount of TB4 in the composition that is administered systemically is at least about 60 µg, is not anticipated by Turischev because Turischev discloses the use of 0.2, 0.8, and 1.6 µg/g of TF5 in rats weighing between 180 and 220 grams, but the only effective dose was 0.8 µg/g. Accordingly, the only effective dose of TF5 administered was 0.8 µg/g x 220 g = 176 µg TF5. As noted above, the attached declaration of Dr. Ehrlich details that TF5 has long been known to contain 0.45 % thymosin beta 4 based on Low et al., *Proceedings of the National Academy of Science*, 1981, page 1163, 1st paragraph of RESULTS. References cited in the declaration that are not already of record in this case are being submitted in an Information Disclosure Statement (IDS) that is being filed concurrently herewith. Accordingly, the amount administered by Turischev to the largest rat was 0.792 µg of thymosin beta 4. Thus,

Turischev does not anticipate or render obvious claim 270. When considered as the dosage of TB4 administered per gram of the subject treated, the dosage administered to the largest rat was 3.6 ng/g. In contrast, the present application discloses dosage administration of 60 µg/220 g = 272.7 ng/g. Further, because Turischev demonstrates that at higher doses of TF5, efficacy is lost, it would not have been routine optimization to increase the dose. Moreover, the dosage recited in claim 267 is almost two orders of magnitude larger than those disclosed in Turischev, which is clearly not a routine modification of drug dosage. Written description support for this subject matter is found in Example 1 on pages 29-32 and Figures 2-4. No new matter has been added.

Turischev discloses that each TF5 dose was diluted in 0.5 mL physiological solution before being administered to the rats (see page 2, 1st full paragraph of the translation provided by the U.S. Patent and Trademark Office). Accordingly, the concentrations of Tβ4 in the compositions administered at the 0.2 µg/g, 0.8 µg/g, and 1.6 µg/g doses to the largest rat were 0.2 µg/500 µL, 0.79 µg/500 µL, and 1.58 µg/500 µL, respectively, i.e., 0.04% w/v, 0.16% w/v, 0.32% w/v, respectively.

Applicants submit that dependent claim 272, which is directed to a method wherein the composition to be administered systemically contains at least 20% thymosin beta 4 (TB4) by w/v, is not anticipated or rendered obvious by Turischev because Turischev discloses the administration of compositions containing at most 0.32 % w/v TB4. Written description support for this subject matter is found in Example 1 on page 29-32 and Figures 2-4. No new matter has been added.

Further, Applicants submit that dependent claim 292, which is directed to a

method wherein the composition is substantially free of other proteins, lipids, or carbohydrates with which TB4 is naturally associated is not anticipated or rendered obvious by Turischev because Turischev only discloses administering TF5, which contains many other naturally associated biological components. Written description support for this subject matter is found, *inter alia*, on page 18, lines 4-6 and compositions used in Example 2. No new matter has been added.

As detailed in Dr. Ehrlich's declaration, attached, Turischev does not anticipate or render obvious the presently claimed invention because a) Turischev demonstrates that the effect of administering TF5 is unpredictable depending on the mode of administration; b) Turischev discloses that the use of TF5 topically was detrimental to the wound healing process in rats; c) Turischev demonstrates that only one out of the three tested dosage amounts of TF5 administered intraperitoneally to the rats, i.e., 0.8 µg/g, had a significant effect on wound healing; d) Turischev demonstrates that increasing or decreasing the sole effective dosage amount resulted in a loss of effectiveness for accelerating wound healing compared to control; e) it was unpredictable, in view of Mann, whether the effect demonstrated by Turischev was attributable to Tβ4, to thymosin alpha 1, or to a combination thereof; and f) Turischev's method is directed specifically to accelerating skin wound healing, but not to a method for promoting tissue repair.

Dr. Ehrlich states that, in his expert opinion, one of ordinary skill reading Turischev as evidenced by Mann, would have found the results confounding and been

unable to extract suggestions for obvious modifications and practical methods of using TF5. Persons of ordinary skill would have found that it was completely unpredictable whether another form or administration of TF5 would have a positive effect (e.g., intrapertioneal at 0.8 µg/g), a negative effect (e.g., topical administration at 0.8 µg/g or 1.6 µg/g), or any effect at all (e.g., intraperitoneal administration at 0.2 µg/g or 1.6 µg/g) on wound healing.

Further, Dr. Ehrlich states that one of ordinary skill reading Turischev as evidenced by Mann, would have been dissuaded from using TF5 topically because Turischev discloses that TF5 administered topically caused "intensification and prolongation of the phase of inflammation" (page 4, lines 15-17), increased suppuration with increased TF5 dosage administered (page 4, lines 13-15), significantly slower healing **and** slower contraction of wounds compared to control (page 3, last two paragraphs), and "a trend toward lengthening of [the period for complete epithelialization (PCE)]" with increasing TF5 dose administered (page 5, lines 1-3).

Accordingly, in the absence of disclosure for effectively using TF5 in any dosage other than 0.8 µg/g and by any method other than intraperitoneally, it is clear that Turischev does not anticipate or even remotely suggest the presently claimed method of promoting repair of a tissue in a subject in need of tissue repair, comprising administering to the subject a composition comprising thymosin beta 4 (TB4) and a pharmaceutically acceptable carrier or vehicle therefore, wherein the composition is administered, either topically or systemically, in an amount effective to repair and revitalize the subject's tissue.

Specifically, Dr. Ehrlich states that, in his expert opinion, persons of ordinary skill, reading Turischev as evidenced by Mann, would have been dissuaded from using TF5 intraperitoneally at a dose other than 0.8 μg/g. Dr. Ehrlich explains that because the experimental results in Turischev demonstrated that dosages of 0.2 μg/g and 1.6 μg/g did not significantly accelerate wound healing compared to control (page 3, lines 5-15), persons of ordinary skill in the art would have found it useless to administer TF5 at a dose lower or higher than 0.8 μg/g.

Further, Dr. Ehrlich states that, in his expert opinion, persons of ordinary skill in the art, reading Turischev as evidenced by Mann, would not have known whether the effect on wounds observed at 0.8 μg/g TF5 was due to the activity of Tβ4, the activity of thymosin alpha 1, or the combined activity of Tβ4 and thymosin alpha 1. This opinion is based on the disclosure in Mann that "Tα1 and Tβ4 have been characterized with regard to their ability to...enhance wound healing...." Col. 4, lines 55-58. Accordingly, Dr. Ehrlich states that persons of ordinary skill in the art reading Mann would have been unable to determine what effect, if any, was attributable to Tβ4 and, therefore, persons of ordinary skill in the art would not have had any guidance as to how to use Tβ4 in a composition, e.g., at what concentration, at what dosage, alone or combined with Tα1 and other thymus ingredients. Accordingly, because of the confounding results reported in Turischev, it is Dr. Ehrlich's expert opinion that Turischev cannot be read as providing anything more than instructions to use TF5 at 0.8 μg/g intraperitoneally and no suggestions for modification or optimization of this method.

Further, Dr. Ehrlich states that a person of ordinary skill in the art, reading Turischev as evidenced by Mann, would have found Turischev's method at odds with a method for promoting tissue repair. In Dr. Ehrlich's opinion, based on evidence in Turischev, there is a technical difference between the terms "wound healing" and "tissue repair." Specifically, Dr. Ehrlich points to the page 4 of the English translation of Turischev, where Turischev discloses that "[t]he use of T in our experiment probably **disrupts the balance of immunological components that is characteristic for repair** by stimulating mononuclear cells, which leads to prolonging of inflammation." Page 4 of the English translation of Turischev (emphasis added). Accordingly, it is Dr. Ehrlich's opinion that persons of ordinary skill in the art, reading Turischev as evidence by Mann, would have understood that TF5 had negative effects on tissue repair. Further, Dr. Ehrlich points out that the method of Turischev has negative effects on tissue repair such as suppuration, which is commonly known as the formation of pus. Dr. Ehrlich explains that when a tissue is suppurative, it recruits and contains large numbers of neutrophils in response to an infection causing inflammation and slowing repair of the tissue. Accordingly, it is Dr. Ehrlich's opinion that because Turischev discloses that topical use of TF5 increased suppuration and that suppuration existed when using TF5 intraperitoneally, persons of ordinary skill in the art would have understood that Turischev's method did not promote tissue repair.

Moreover, Dr. Ehrlich explains that experimental evidence has shown that administration of a composition containing synthetic Tβ4 decreases neutrophil recruitment and is characterized by a lack of suppuration, based on articles by Young et

al. and Sosne et al. References cited in the declaration that are not already of record in this case are being submitted in an Information Disclosure Statement (IDS) that is being filed concurrently herewith. Accordingly, Dr. Ehrlich points out that the use of compositions according to the present invention have been found to be antimicrobial and no suppuration has been reported when administering the composition to any subject, including rats, mice, and human subjects.

It is Dr. Ehrlich's expert opinion that, because Turischev disclosed that TF5 was only effective at a dose of 0.8 µg/g TF5, i.e., 3.6 ng/g Tβ4, when administered intraperitoneally, it clearly did not disclose administering greater than 6 µg, i.e., 27.3 ng/g Tβ4, intraperitoneally, and taught away from modifications such as increasing or decreasing the dosage because 1.6 µg/g TF5, i.e., 7.2 ng/g Tβ4, or 0.2 µg/g TF5, i.e., 0.9 ng/g Tβ4, **were both ineffective**.

Further, it is Dr. Ehrlich's expert opinion that persons of ordinary skill in the art reading Turischev as evidenced by Mann would not have known or been able to predict that a composition containing Tβ4 could have a positive tissue repair effect when administered topically **at any** concentration. Rather, Dr. Ehrlich states that it is clear that persons of ordinary skill in the art would have learned to avoid using TF5 topically after reading Turischev because Turischev showed that TF5 causes "intensification and prolongation of the phase of inflammation" (page 4, lines 15-17), increased suppuration with increased TF5 dosage administered (page 4, lines 13-15), significantly slower healing and slower contraction of wounds compared to control (page 3, last two paragraphs), and "a trend toward lengthening of [the period for complete

epithelialization (PCE)]" with increasing TF5 dose administered (page 5, lines 1-3).

Dependent claims 266 and 293 further define the invention so that the TB4 to be administered is synthetic. As is clear from above, experimental evidence has shown that the method according to claims 266 and 293 has unexpected advantages. For example, the administration of a composition containing synthetic TB4 has been shown to not cause antibody genesis, to not cause suppuration, and to be antimicrobial. In contrast, Turischev reported significant suppuration when administering TF5 both topically (reported as the stimulation of mononuclear cell recruitment, which leads to prolonging of inflammation) and intraperitoneally. *See* paragraph bridging pages 3-4 and page 4, 2nd full paragraph of the English translation of Turischev. Accordingly, Applicants submit that claims 266 and 293, which are directed to administration of synthetic TB4, are distinguished over Turischev.

Applicants submit that independent method claim 237 is not anticipated or rendered obvious by Turischev, as evidenced by Mann for the following reasons:

1. Turischev does not disclose a method of promoting repair of a tissue in a subject in need of tissue repair;

2. Turischev does not disclose promoting repair of a tissue in a subject in need of tissue repair by topically administering to said subject a composition comprising thymosin beta 4 (TB4);

3. Turischev does not disclose promoting repair of a tissue in a subject in need of tissue repair by topically administering to said subject a composition comprising a pharmaceutically acceptable carrier or vehicle therefore;

4. Turischev does not disclose promoting repair of a tissue in a subject in need of tissue repair wherein by topically administering to said subject a composition in an amount effective to

a) repair **and**

b) revitalize

said subject's tissue.

Further, independent method claim 267 is not anticipated or rendered obvious by Turischev, as evidenced by Mann for the following reasons:

1. Turischev does not disclose a method of promoting repair of a tissue in a subject in need of tissue repair;

2. Turischev does not disclose promoting repair of a tissue in a subject in need of tissue repair by systemically administering greater than 6 µg thymosin beta 4 (TB4) in a composition to the subject;

3. Turischev does not disclose promoting repair of a tissue in a subject in need of tissue repair by systemically administering to the subject a TB4 composition comprising a pharmaceutically acceptable carrier or vehicle therefore;

4. Turischev does not disclose promoting repair of a tissue in a subject in need of tissue repair wherein by systemically administering to said subject a composition in an amount effective to

a) repair **and**

b) revitalize,

said subject's tissue.

Accordingly, Applicants submit that Turischev does not anticipate or render obvious the present claims and respectfully request that the rejections be withdrawn.

Response to Rejections under 35 U.S.C. § 103

Claims 187-188, 191-196, 198-200, 202-205, 208-213, 215-217, 219-221, and 223 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Turischev and Mann and Puolakkainen. Insofar as this rejection could apply to the present claims, it is respectfully traversed.

The Office Action acknowledges that Turischev does not disclose transforming growth factor beta, recombinant or synthetic TB4, or sterile water as a carrier. However, the Office Action asserts that one of ordinary skill would have found it obvious to use sterile water to ensure that there is no unnecessary contamination. The Office Action asserts that Puolakkainen discloses that TGF-beta is known to enhance wound healing and it would have been obvious to combine Puolakkainen with Turischev to add TGF-beta to the TF5 composition of Turischev. Further, the Office Action asserts that Puolakkainen discloses recombinant TGF-beta and thus it would have been obvious to use recombinant proteins.

Applicants submit that the rejected claims have been cancelled and replaced with the above new claims. For the reasons outlined above, Applicants have shown that independent claims 237 and 267 are not anticipated or rendered obvious by Turischev, as evidenced by Mann. Puolakkainen does not remedy the deficiencies of Turischev because Puolakkainen is only related to administering TGF-beta. Accordingly, claims depending from independent claims 237 and 267 are distinguished for at least the above reasons.

With regard to sterile water, Applicants submit that Turischev only discloses the use of physiological solution (see page 2). Sterile water is not the same as physiological solution because it lacks the buffering ability of physiological solution. Accordingly, one of ordinary skill in the art reading Turischev would not have found it obvious to dilute a small amount of a cellular fraction in a relatively larger amount of sterile water (because Turischev disclosed diluting the fraction in 0.5 mL of solution) as it would have almost certainly cause precipitation of various cellular components, e.g., proteins. Moreover, the term 'solution' means that a substance is homogeneously dissolved in another substance. Sterile water is not any kind of solution, thus it is improper to even suggest that one of ordinary skill in the art reading Turischev would have found it obvious to substitute sterile water for a physiological solution when diluting a cellular fraction.

Further, Applicants respectfully submit that Puolakkainen only discloses that the TGF-beta be recombinant, whereas instant dependent claims 244 and 278 recite that the TB4 is recombinant. Accordingly, Applicants submit that Puolakkainen does not disclose or suggest using recombinant TB4.

Accordingly, based on the above reasons, Applicants respectfully request that all rejections under the combination of Turischev, Mann, and Puolakkainen be withdrawn.

Claims 187-188, 191-196, 200, 202-205, 208-213, 217, 219-221, and 223 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Malinda et al., Baumann et al., and Biotech Patent News. Insofar as this rejection could apply to the present claims, it is respectfully traversed.

The Office Action asserts that Malinda discloses that Thymosin beta 4 (TB4) acts as a chemoattractant for endothelial cells, in vitro wound closure is more rapid in the presence of TB4, cell migration is enhanced by TB4, TB4 is important in angiogenesis and that the formation of blood vessels and is an important part of wound healing, others report that TB4 could play a major role in would healing. The Office Action acknowledges that Malinda does not disclose administering TB4 to subjects in need of wound repair. The Office Action asserts that Baumann discloses that TB4 leads to an increase in wound healing in vitro, and that Biotech Patent News discloses that investigators will use thymosin beta 4 in a wound healing study. The Office Action asserts that one would be motivated to use TB4 specifically for those with wounds based on the combination of Malinda, Baumann and Biotech Patent News. Applicants submit that the cited combination of references do not render the present claims obvious.

Malinda relates to cell migration studies and a wound closure assay using HUVEC monolayers. The disclosure of Malinda does not disclose or suggest the presently claimed method because Malinda does not relate to a method of promoting repair of a tissue in a subject in need of tissue repair, comprising administering to the subject a composition comprising thymosin beta 4 (TB4) and a pharmaceutically acceptable carrier or vehicle therefore, wherein the composition is administered in an amount effective to repair and revitalize the subject's tissue. Malinda does not disclose administration of TB4 for treating, effecting, or promoting any condition. Tissue repair is

not mentioned in Malinda. Further, Malinda is silent as to administering a composition in an amount effective to repair **and** revitalize tissue.

Applicants submit that Baumann does not add any relevant disclosure or suggestion to the disclosure of Malinda. The only instance where 'wound healing' is disclosed in Baumann is in Table II on page 21, where it is classified as an *in vitro* activity of TB4. Table II specifically lists ***in vivo*** functions of TB4 such as induction of TdT activity in TdT negative cells, increases TdT activity in hydrocortisone immunosuppressed mice, stimulation of pituitary secretion of luteinizing hormone, stimulation of hypothalamic release of luteinizing hormone-releasing factor, reduces the toxicity of chemotherapy in mice, and increases angiogenesis. Accordingly, it is clear that Baumann's disclosure not only does not disclose or suggest the presently claimed methods, but it also demonstrates that the activity of TB4 for *in vivo* wound healing was unrecognized at the time of publication. Otherwise, Baumann would have included wound healing activity as an *in vivo* activity as well. It follows then that, because the in vivo effects of TB4 were unknown and unpredictable, Biotech Patent News, which is a press release referring to the Applicants' own work, states that studies with wound healing were ongoing. Applicants submit that all of the Malinda, Baumann, and Biotech Patent News references make cursory allusions to Applicants' own work. However, the combination of these publications does not suggest the presently claimed method. Persons of ordinary skill, reading the cited combination, would not arrive at the presently claimed method. Independent method claim 237 is not rendered obvious by the combination of Malinda, Baumann, and Biotech Patent News for the following

reasons:

1. The combination does not mention or suggest a method of promoting repair of a tissue in a subject in need of tissue repair (a wound closure assay in HUVEC cells does not suggest or relate to promoting tissue repair in a subject);

2. The combination does not mention or suggest promoting repair of a tissue in a subject in need of tissue repair by topically administering to said subject a composition comprising thymosin beta 4 (TB4) (an in vitro wound closure assay is insufficient to provide a reasonable expectation of success when topically administering to a subject as is clearly shown by the failure of Turischev);

3. The combination does not mention or suggest promoting repair of a tissue in a subject in need of tissue repair by topically administering to said subject a composition comprising a pharmaceutically acceptable carrier or vehicle therefore;

4. The combination does not mention or suggest promoting repair of a tissue in a subject in need of tissue repair wherein by topically administering to said subject a composition in an amount effective to

a) repair **and**

b) revitalize

said subject's tissue.

Further, independent method claim 267 is not rendered obvious by the combination of Malinda, Baumann, and Biotech Patent News for the following reasons:

1. The combination does not mention or suggest a method of promoting repair of a tissue in a subject in need of tissue repair (a wound closure assay in HUVEC cells does not suggest or relate to promoting tissue repair in a subject);

2. The combination does not mention or suggest promoting repair of a tissue in a subject in need of tissue repair by systemically administering greater than 6 µg thymosin beta 4 (TB4) in a composition to the subject (an in vitro wound closure assay is insufficient to provide a reasonable expectation of success when systemically administering drugs to a subject as is clearly shown by the failure of Turischev);

3. The combination does not mention or suggest promoting repair of a tissue in a subject in need of tissue repair by systemically administering to said subject a composition comprising a pharmaceutically acceptable carrier or vehicle therefore;

4. The combination does not mention or suggest promoting repair of a tissue in a subject in need of tissue repair wherein by systemically administering to said subject a composition in an amount effective to

a) repair **and**

b) revitalize

said subject's tissue.

Claims 187-188,191-196,198-200,202-205,208-213,215-217,219-221,223 were rejected under 35 U.S.C. 103(a) as being unpatentable over Malinda, Baumann,

Biotech Patent News, and Puolakkainen. Insofar as this rejection could apply to the present claims, it is respectfully traversed.

The Office Action acknowledges that none of Malinda, Baumann, and Biotech Patent News discloses or suggests the use of TGF-beta, but asserts that Puolakkainen discloses that TGF-beta is known to enhance wound healing and asserts that one would be motivated to use the disclosure of Puolakkainen along with the other references for wound healing. Applicants submit that the combination of Malinda, Baumann, and Biotech Patent News does not render independent claims 237 and 267 obvious for at least the above reasons. Puolakkainen does not remedy the deficiencies of the combination of combination of Malinda, Baumann, and Biotech Patent News because it relates only to TGF-beta. Accordingly, Applicants submit that the present claims are not rendered obvious by the cited combination.

Response to Provisional Double Patenting Rejections

Claims 187-188, 191-193, 195-196, 198, 200, 202-205, 208-210, 212-213, 215-217, 219-220, and 223 remained provisionally rejected under doctrine of non-statutory double patenting over claims in three separate co-pending patent applications. Applicants continue to request that all provisional rejections on grounds of double patenting be held in abeyance until such claims have been indicated to be allowable and it becomes possible to determine whether claims directed to the same invention or an obvious variant thereof would be issued in more than one patent.

Conclusions

In light of the foregoing, Applicants submit that all outstanding rejections have been overcome. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all the outstanding rejections. Early and favorable action is awaited.

The Commissioner is hereby authorized to charge any fees and to credit any overpayments that may be required with respect to this paper to Counsel's Deposit Account No.02-2135.

Respectfully submitted,

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